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Long-term outcome after sequential liver and lung metastasectomy is comparable to outcome of isolated liver or lung metastasectomy in colorectal carcinoma

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ABSTRACT

Background and aims: Previously, colorectal cancer (CRC) metastasis of both liver and lungs was considered disseminated disease, which contraindicated surgical metastasectomies. Increasing evidence from studies on patient series have indicated that survival improved after resecting both liver and lung metastases. However, those results and long-term outcomes remain controversial. We aimed to compare surgical outcomes between patients treated for both liver and lung metastases to the patients who had only isolated liver or lung metastases.
Material and methods: All patients (n = 105) underwent surgery for CRC metastases between July 2002 and September 2015. Three groups were compared: the sequentially operated group (n = 33 patients) underwent sequential liver and lung resections; the liver group (n = 38 patients) underwent liver resections; and the lung group (n = 34 patients) underwent lung resections. The main endpoints were long-term survival rates.
Results: The groups were not different in disease-free survival (P = 0.727) or overall survival (P = 0.218). Five-year survival rates were 69.7% in the sequentially operated group, 65.1% in the liver group, and 50.0% in the lung group.
Conclusion: Long-term outcomes after sequential liver and lung resections of CRC metastases were comparable to outcomes after isolated liver or lung metastasectomies. Therefore, aggressive surgical interventions should be considered for patients with both liver and lung metastases of CRC.

1. Introduction

Colorectal carcinoma (CRC) is the third most common cancer worldwide, and the most common metastatic sites are liver and lungs [1,2]. Approximately half of the patients with CRC develop liver metastases [1,3] and 8–20% develops lung metastases [4–6]. Recent studies have shown that surgical resection is the most efficient treatment of isolated liver or lung metastasis. After liver resections, the 5-year survival rates were up to 58% [7–10] and 10-year survival rates were up to 25–28% [9,11]. After lung resections, the 5-year survival rates were 36–45% [1,10,12–14].

Previously, colorectal cancer metastasis to both liver and lungs was considered disseminated disease, and therefore, inoperable. Several recent patient series studies have reported improved survival after sequential resections of liver and lung metastases; the 5-year survival rates ranged from 30 to 70% [1,2,4,10,12,13,15–19]. Modern chemotherapy, and possibly biological agents, have played a major role in improving long-term outcomes after sequential liver and lung resections [1]. However, the reported survival rates vary considerably, and surgical treatment of patients with CRC liver and lung metastases has been challenged, due to controversial outcomes [16,20,21]. Different studies are difficult to compare, due to the differences in study plans, outcome measurements (e.g., starting from the first or last metastasectomy), and selection biases.

The present study aimed to compare matched patient groups with CRC metastases. In the first group, patients had both liver and lung metastases and underwent sequential liver and lung resections. In the second group, patients had isolated liver metastases and underwent liver resection(s). In the third group, patients had isolated lung metastases and underwent lung resection(s). We compared differences in overall survival (OS, primary endpoint) and disease-free survival (DFS, secondary endpoint) between these three groups.

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2. Materials and methods

2.1. Materials and methods

All patients underwent lung and/or liver metastasectomies of colorectal carcinoma metastases with a curative intent at Helsinki University Hospital between July 2002 and September 2015. In the present study, all data were retrospectively collected and analyzed to define long-term outcomes.

Three groups were compared: the sequentially operated group consisted of patients (n = 33) that underwent both liver and lung metastasectomies. In this group, metastases in liver and lung were diagnosed synchronously or sequentially. Two control groups comprised: the liver group consisted of patients with isolated, resectable liver metastases (n = 38); and the lung group consisted of patients with isolated, resectable lung metastases (n = 34). For the control groups, patients were selected as near as possible to the same time period, to correspond patients in the sequentially operated group. Control and study group patients were also matched for the age. All patients received neoadjuvant and/or adjuvant chemotherapy. Twenty-two patients underwent re-resections, due to recurrent metastases, and these operations were included in the analyses.

The following demographic data were collected: age and sex; location of primary tumor (colon/rectum); nodal involvement, and metastasis classification system (pTNM-staging); synchronous versus metachronous metastases; and mutation status (KRAS, BRAF), when available. The number and sizes of metastases and tumor characteristics were also collected based on the pathological analyses and analyzed. For the liver metastases, vascular, neural, and biliary invasions were evaluated by experienced histopathologists.

Metastases were considered synchronous when diagnosed within 6 months after the primary colorectal cancer diagnosis.

Decisions on the surgical and oncological treatments were made by the multidisciplinary team (MDT).

Resectability of liver metastases was determined in MDT. Resection should achieve negative resection margins while preserving future liver remnant at least 30% of the total estimated liver volume and sparing at least two segments and maintaining vascular inflow and outflow and biliary drainage.

Lung metastases were considered resectable if R0 resection was possible without pulmonectomy and patients had no extrathoracic disease. Bilateral metastases were not contraindication. If synchronous liver and lung metastases, liver was operated at the first.

DFS was defined as the time interval between the last metastasectomy and recurrence, death or last follow-up. OS was defined as the time interval from the first metastasectomy to the date of death or last follow-up.

2.2. Statistics

Data were analyzed with IBM SPSS software version 22.0 (United States). Demographics and histopathological details were compared between groups with the Chi-square test, Fisher's test, One-Way ANOVA, or Kruskal Wallis' test, as appropriate. DFS and OS were analyzed with the Kaplan-Meier estimation method. Survival rates were compared between groups with the log-rank test. P-values less than 0.05 were considered significant.

3. Results

A total of 105 patients were included in this study. Demographic data are presented in Table 1. The median follow-up times were 67.1 months (range:7.1–163.0) for all patients; 65.8 months (range 14.9–162.8) for the sequentially operated group; 81.6 months (range 7.1–163.0) for the liver group; and 56.4 months (range 10.8–138.8, n.s.) for the lung group. Twenty-two patients received multiple operations.

Table 1
Demographics of the three groups of patients that underwent surgery for colorectal cancer metastases.

Characteristic	Group 1 Resected liver and lung metastases, n = 33	Group 2 Resected liver metastases, n = 38	Group 3 Resected lung metastases, n = 34	p-value
Age, years (median, range)	65.0 (36–80)	60.0 (32–82)	61.0 (38–78)	0.677
Gender				0.362
male	20 (60.6%)	24 (63.2%)	16 (47.1%)	
female	13 (39.4%)	14 (36.8%)	18 (52.9%)	
Primary tumor				0.003
rectum	19 (57.6%)	15 (39.5%)	27 (79.4%)	
colon	14 (42.4%)	23 (60.5%)	7 (20.6%)	
T1-2	4 (12.5%)	5 (15.6%)	5 (14.3%)	0.999
T3-4	28 (87.5%)	30 (85.7%)	27 (84.4%)	
Node status				0.285
N0	10 (31.3%)	18 (51.4%)	15 (45.5%)	
N1	11 (34.4%)	12 (34.3%)	12 (36.4%)	
N2	11 (34.4%)	5 (14.3%)	6 (18.2%)	
Synchronous				0.008
yes	24 (72.7%)	19 (50.0%)	12 (35.3%)	
no	9 (27.3%)	19 (50.0%)	22 (64.7%)	
KRAS				0.021
Wild type	17 (65.4%)	11 (73.3%)	7 (31.8%)	
Mutation	9 (34.6%)	4 (26.7%)[a]	15 (68.2%)[b]	

Values are the number of patients (%), unless otherwise indicated. [a]Compared to group 1: P = 0.734; [b]Compared to group 1: P = 0.041; KRAS: Kirsten rat sarcoma virus oncogene involved in regulating cell division.

Table 2
Comparison of histological characteristics of liver metastases between patients with A. combined metastases and B. patients with only liver metastases.

Characteristic	A. Patients (n = 33) with total of 40 liver resections	B. Patients (n = 38) with total of 50 liver resections	p-value
Number of metastases			0.999
≤ 2	29 (74.4%)	38 (76.0%)	
> 2	10 (25.6%)	12 (24.0%)	
Size of the largest metastases			0.824
≤ 30 mm	24 (61.5%)	33 (66.0%)	
> 30 mm	15 (38.5%)	17 (34.0%)	
Vitality			0.359
< 50%	16 (44.4%)	15 (32.6%)	
≥ 50%	20 (55.6%)	31 (67.4%)	
Invasion[a]			0.259
yes	0	3 (6.1%)	
no	36 (100.0%)	46 (93.9%)	
Extent of resections			0.382
minor	20 (52.6%)	32 (64.0%)	
major	18 (47.4%)	18 (36.0%)	
Residual tumor			0.289
R0	36 (94.7%)	43 (86.0%)	
R1	2 (5.3%)	7 (14.0%)	
Complications[b]			0.999
yes	3 (7.5%)	4 (8.2%)	
no	37 (92.5%)	45 (91.8%)	

[a] Biliary, nervous, and/or vascular invasion.
[b] Pulmonary embolism, deep vein thrombosis, pneumonia and/or biloma.

3.1. The primary tumor

The primary tumor locations were significantly different between the three groups. Primary tumors in the rectum were observed in the majority of patients (79.4%) with lung metastases, but in less than half (39.5%) of the liver resection group, and in 57.6% of the sequentially operated group (p = 0.003) (Table 1). Metastases were synchronous

Table 3
Comparison of histological characteristics of lung metastases between A. patients with combined metastases and B. patients with only lung metastases.

Characteristic	A.Patients (n = 33) with total of 49 lung resections	B. Patients (n = 34) with total of 53 lung resections	p-value
Site of lung metastases			0.309
right	27 (55.1%)	24 (45.3%)	
left	16 (32.7%)	25 (47.2%)	
both	6 (12.2%)	4 (7.5%)	
Resection type			0.523
wedge	32 (65.3%)	29 (54.7%)	
segmentectomy	11 (22.4%)	14 (26.4%)	
lobectomy	6 (12.2%)	10 (18.9%)	
Surgical techniques			0.207
thoracotomy	16 (32.7%)	26 (49.1%)	
VATS	30 (61.2%)	26 (49.1%)	
both	3 (6.1%)	1 (1.9%)	
Number of metastases			0.828
1	33 (70.2%)	34 (66.7%)	
≥ 2	14 (29.8%)	17 (33.3%)	
Size of the largest metastasis			0.213
≤ 15 mm	31 (67.4%)	27 (52.9%)	
> 15 mm	15 (32.6%)	24 (47.1%)	
Complications[a]			0.424
yes	4 (8.2%)	2 (3.8%)	
no	45 (91.8%)	51 (96.2%)	

[a] Complications: pneumonia, empyema, deep vein thrombosis; VATS: Video-assisted thoracoscopic surgery.

with the primary tumor in 72.7% of the sequentially operated group, 50.0% of the liver group, and 35.3% of the lung group (p = 0.008).

3.2. Tumor stages

Tumor stages are shown in Table 1. T-stage or the node status of the primary tumor were not significantly different between the three groups (p = 0,999 and p = 0.285, respectively). Most patients had T3-stage disease, including 71.3% of the sequentially operated group, 65.7% of the liver group, and 78.1% of the lung group. The N0-stage was found in 31.3% of the sequentially operated group, 51.4% of the liver group, and 45.5% of the lung group.

3.3. Mutation status

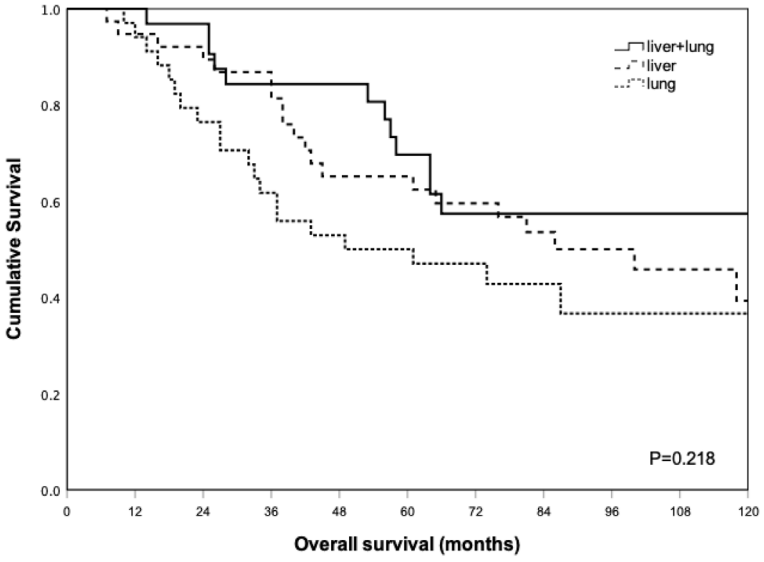
The results of mutation analyses are shown in Table 1. The patients were not consistently tested for KRAS mutations. The prevalence of the KRAS mutation was significantly higher in the lung group (68.2%) than in the sequentially operated group (34.6%) and the liver group (26.7%; p = 0.021). Only one patient had BRAF mutation among the tested patient. This patient had liver and lung metastases and is now alive and recurrence-free.

3.4. Histopathology

Histopathological findings on the resected liver and lung metastases are shown in Tables 2 and 3, respectively. We found no significant differences in any histological characteristics.

3.5. Complications

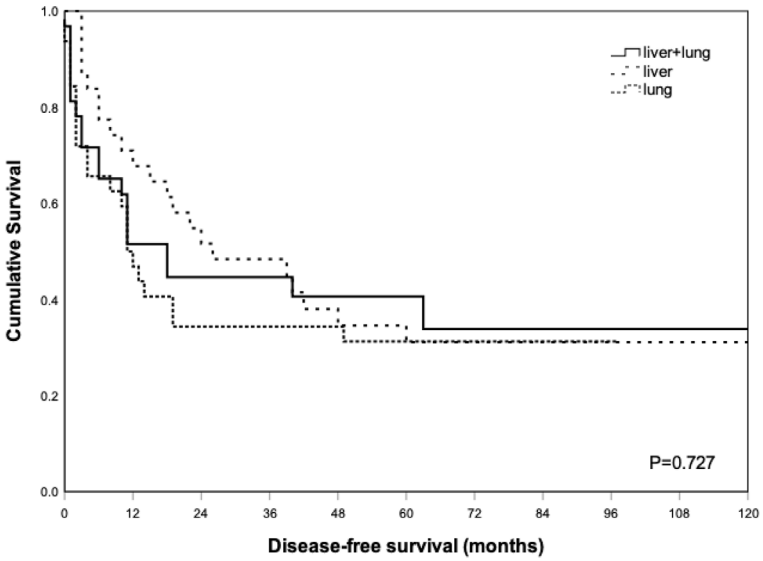
The rate of complications was similar between the sequentially operated and liver groups (Table 2). The most common complications



Number at risk:

	Total	12months	24months	36months	48months	60months	72months	84 months
Liver + lung	31	31	31	25	23	18	11	8
Liver	37	36	34	30	24	24	21	15
Lung	33	32	26	21	18	17	12	7

Figure 1. Overall survival.



Number at risk:

	Total	12months	24months	36months	48months	60months	72months	84 months
Liver + lung	31	15	12	11	8	6	5	3
Liver	30	21	16	14	10	9	8	5
Lung	31	15	11	11	11	9	4	3

Fig. 2. Disease-free Survival counted from the last metastasectomy.

were pulmonary embolism, deep vein thrombosis, and pneumonia. One patient developed a postoperative biloma.

The sequentially operated and lung metastases groups also had similar rates of complications (Table 3). The most common complications were pneumonia, empyema, and deep vein thrombosis.

3.6. Time intervals between metastasectomies

The median time intervals between the first and second metastasectomies were 15.4 months (range: 1.2–67.4) for the sequentially operated group (n = 33), 14.5 months (range: 1.9–69.7) for the liver group (n = 38), and 4.9 months (range: 0.7–35.5) the lung group (n = 34). The time intervals between the second and third metastasectomies were 14.5 months (range: 3.7–31.2) for the sequentially operated group (n = 33), 19.7 months (range: 8.9–63.5) for the liver group (n = 38), and 6.5 months (range: 2.6–17.2) for the lung group (n = 34).

3.7. Overall and disease-free survival rates

The OS was evaluated starting from the first metastasectomy. The DFS was evaluated starting from the last metastasectomy. The median OS rates were 133.0 months in the sequentially operated group, 100.0 months in the liver group, and 49.0 months in the lung group (Fig. 1). The median DFS rates were 18.0 months in the sequentially operated group, 26.0 months in the liver group, and 11.0 months in the lung group (Fig. 2). The three groups were not significantly different in either DFS (p = 0.727) or OS (p = 0.218).

The 1-, 3-, and 5-year OS rates were 100.0%, 84.4%, and 69.7%, respectively, in the sequentially operated group; 94.7%, 81.4%, and 65.1%, respectively, in the liver group; and 94.1%, 61.8%, and 50.0%, respectively, in the lung group: (n.s).

4. Discussion

Surgical resection of isolated liver or lung metastasis is the standard treatment in metastatic colorectal carcinoma, but the long-term outcome of patients that require resections of both liver and lung metastases had not been established. In the present study, we analyzed long-term survival of patients that underwent sequential liver and lung resections compared to patients that underwent either isolated liver or isolated lung resections.

We found that the 5-year OS was 69.7% for patients in the sequentially operated group. In previous studies, 5-year OS rates were reported to be 40.7–77.5% [2,10,12,15,18,19,22–24]. The variation in reported survival rates was partly due to different starting times for the calculations. OS times were counted starting from the last metastasectomy in Brouquet et al. [2], from the liver resection in Andres et al. [18], and from the resection of the primary tumor in Limmer et al. [15]. Only Marudanayagam et al. [12] counted OS times from the first metastasectomy, which was the method used in the present study. The higher OS in the present study was most likely due to strict patient selection. Marin et al. [10] found that patient selection significantly affected the survival results [10]. In some earlier studies, historical controls were used for comparisons [1,10,16], or there was no control group at all [1,4,12]. On systematic review and meta-analysis of Gonzalez et al. [25] previously resected liver metastases did not effect on OS rates with patients who underwent lung metastasectomy.

Surprisingly, in the present study, survival rates did not differ among the three groups. Marudanayagam et al. [12] and Andres et al. [18] compared survival after sequential liver and lung resections to survival after isolated liver resections. They reported similar survival

rates between these groups. Brouquet et al. [2], reported that patients with colorectal cancer metastases showed better survival rates after sequential liver and lung resections (50% survived for 5 years), compared to survival after isolated liver resections (40% survived for 5 years). However, those results might have been slightly biased, because the control group consisted of a large, unselected population of patients that underwent liver resections over a long time period.

Hattori et al. [13] found that OS after an isolated pulmonary metastasectomy was significantly better than after sequential liver and lung metastasectomies, although the DFS was similar. Landes at al [16] reported that, a prior liver resection was an adverse prognostic factor for survival after a pulmonary metastasectomy compared to survival without a prior liver resection.

In the present study, recurrence rates were quite similar between the three groups; the 5-year DFS varied between 31 and 41%. Brouquet et al. [2] reported 25% DFS for patients with sequential liver and lung resections, and Andres et al. [18] found 5-year DFS in 31.0% of patients with liver resections and only 12.9% of patients with both liver and lung resections. Differences between studies might have been due to a selection bias.

The KRAS mutation rate was highest in patients with lung resections, perhaps reflecting the slightly, but not significantly, lower survival rate in the lung group compared to the other two groups. KRAS mutations were reported to be associated with worse DFS and OS rates [26,27].

Our finding that patients with lung resections had the highest proportion of rectal primary tumors was noted in earlier studies [28]. At least partly, this association might be due to the venous drainage from the distal rectum to the vena cava inferior; and also due to differences in molecular patterns between rectal and colonic cancers [29].

The high rate of synchronous metastases in the sequentially operated group might be a result of selection bias, because multiple metastasis sites indicate more aggressive disease. However, synchronicity did not affect survival rates in this study. All treatment decisions were evaluated by a multidisciplinary team and were based on the recommendations published in a recent consensus statement [30].

The limitations of the present study included relatively small number of patients in each group and its retrospective nature. We intended to minimize selection bias by matching the patients in each group within the same time period. Patients in the liver group were better matched to the study group, because there were more patients in the liver group. The groups differed significantly in the KRAS mutation status, primary tumor location, and synchronous vs. metachronous presentation.

In conclusion, we showed that, in patients with concomitant liver and lung metastases of colorectal cancer origin, a curative surgical approach gave a good long-term outcome, comparable to those achieved with isolated liver and lung resections. Thus, combined metastases in liver and lung should not contraindicate resection. Treatment options should be based on the resectability of the metastases and a history of appropriate chemotherapy.

Declaration of conflicting interests

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2019.05.015.

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